THE EFFECT OF TREATMENT FOR SYPHILIS ON SEVERE ANEMIAS

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FOURNIER in reviewing the anemias of syphilis states that the disease causes a diminution in the percentage of hemoglobin, a decrease in the number of erythrocytes and an increase in the number of leukocytes. He recognizes five types of anemia in association with the disease: (1) the simple secondary anemia (by far the most common), (2) chlorotic anemia, (3) chlorotic anemia with leukocytosis, (4) leukemia and (5) (infinitely rare) syphilis imitating the picture of pernicious anemia.

Fournier refers to the difficulty in some cases of deciding whether syphilis is the direct cause of these modifications or whether they are the result of associated symptoms (the febrile state, symptoms of dyspepsia, nervous troubles, superimposed infections or the influence of misguided therapy). He quotes the old saying that "mercury is the iron of syphilitic anemia." However, after having corrected the syphilitic changes, mercury becomes, in turn, an alterant of the blood. For a time it does good, later it becomes harmful. Mercury cannot be given over a prolonged period without damage. Fournier instituted, therefore, the "method of successive or intermittent treatments."

Since Fournier's time little has been added to our knowledge of the mercurial therapy of syphilitic anemias. The advent of arsphenamin has brought new possibilities, which, although extensively discussed in the abstract, have been reinforced by only a small body of clinical material. This paucity of clinical discussion may be ascribable to the comparative rarity of pernicious anemia in combination with syphilis. The total number of cases with or without syphilis treated with arsphenamin which have been collected from the literature is thirty-six. To this are now added the twenty-five cases of severe anemia which form the basis of the present study. Primary emphasis is laid on the effect of arsphenamin therapy, since the cases were originally approached from this angle.

REVIEW OF LITERATURE

Arsenic was first used in treating pernicious anemia with gratifying results in 1875 by Bramwell. In 1911 he began using arsphen-

amin, one to four injections of 0.3 gm. each intramuscularly, because he desired to secure a gradual and prolonged action of the arsenic constituent of the drug. In 1913 he reported his experience with twelve patients, of whom two showed no change, three showed slight improvement and seven were greatly benefited, although one had a relapse later.

Leede, in 1911, treated five patients with pernicious anemia *in extremis*. Four of them died in from thirty-six hours to fourteen days, and Leede therefore concludes that arsphenamin is directly contraindicated. He also reported a case that gave the impression of pernicious anemia, atypical however. A diagnosis of anemia with a syphilitic basis was made. After one injection the hemoglobin rose from 15 per cent to 60 per cent and the erythrocytes from 900,000 to 4,000,000 in two months. The hemoglobin fell to 50 per cent and a second injection was given; the hemoglobin then rose to 70 per cent in eight days. Leede pointed out the need for splitting up pernicious anemia into further groups (due to *Bothriocephalus latus, Ankylostoma, and so forth*).

Steyrer, in 1912, after treating a patient for some time with Fowler's solution and seeing no improvement, gave several injections of arsphenamin. The hemoglobin rose from 20 per cent to 70 per cent, and the erythrocytes from 700,000 to 4,500,000, with the disappearance of megaloblasts and poikilocytosis.

Friedlander, in 1912, reported a case in which the patient had received large quantities of arsenic and iron. The erythrocytes numbered only 887,000 with 20 per cent hemoglobin, giving an index of 1.1. After two injections of 0.3 gm. arsphenamin and injections of 1 gr. of cacodylate of iron on alternate days for twenty-seven days the erythrocytes rose to 3,200,000, the hemoglobin to 52 per cent, with an index of 0.7, the picture of only a mild anemia.

Hobhouse, in 1912, added one case to the list. His patient had been anemic for more than a year and had improved under large doses of arsenic. In October there was no sign of pernicious anemia, but in May the count showed 800,000 erythrocytes and 18 per cent hemoglobin, with an index of 1. Two intramuscular injections of 0.3 gm. of arsphenamin were given and in October the erythrocytes numbered 4,704,000, hemoglobin 110 per cent, with an index of 1.05.

Boggs, in 1913, reported eleven cases. Three of the patients died. One was moribund at the time of injection and one died eleven days after the administration of 0.2 gm. of arsphenamin. The reaction was not marked and the blood count did not drop more than 200,000 erythrocytes. The third patient improved, the count rose from 1,100,000 to 3,400,000 in twenty days, eventually reaching 4,800,000, with 85 per cent hemoglobin; the patient, however, died later. The picture was never free from the qualitative changes of pernicious anemia. Five patients improved with an initial drop of never more than 200,000 erythrocytes. One received 0.3 gm. intravenously

every four weeks. In sixteen weeks the erythrocytes rose from 500,000 to 5,000,000 and the hemoglobin from 23 per cent to 90 per cent. Two other patients had an average rise of 2,000,000 erythrocytes. Although all precautions were observed a sharp febrile reaction after each injection lasted from six to twelve hours, in contrast to the very mild or absent reactions in syphilities. Boggs concludes that the drug may be given without serious risk, and the results justify its use in pernicious anemia.

Maynard, in 1913, noted a slight increase in erythrocytes after a first injection of arsphenamin; after a second, however, there was a decrease, and he did not use it further.

Weicksel (1913) thinks that syphilitic pernicious anemia is not the result of syphilis, but that under certain predisposing conditions syphilis sometimes leads to this disease. According to him syphilitic anemia is seen in general in latent syphilis. He reports one case, that of a man, aged fifty-two years, with a moderately positive Wassermann reaction and a typical pernicious anemia. The patient was given two injections of arsphenamin and reactions followed which confined him to bed. The erythrocytes subsequently rose from 1,680,000 to 3,700,000 and the hemoglobin from 45 per cent to 85 per cent; the index fell from 1.34 to 1.08. This, however, brings up the question of whether arsphenamin produced the improvement or the collateral treatment for the pneumonia which developed. In the syphilitic pernicious anemia the situation is more favorable, because there is a remedy against the syphilis. Weicksel, in a second article (1913), reported the death of the patient and the pathologic findings of pernicious anemia. Either the old syphilis had no connection with the anemia and the condition was a so-called cryptogenetic form of pernicious anemia or the anemia was the result of a former syphilis for which insufficient arsphenamin had been given to remove the cause. Weicksel inclines to the latter view and advises the use of arsphenamin in further cases.

Lämpe, in 1916, treated three patients suffering from pernicious anemia by the intravenous injections of small doses of arsphenamin, 0.05 gm. to 0.15 gm.; the hemoglobin rose 40 or 50 per cent and the erythrocytes were increased 2,500,000. One of the patients had a remission and died. Lämpe states that he has never seen similar favorable results in cases of pernicious anemia that have been treated in other ways.

Lowrey, in 1917, reported a case in which pernicious anemia developed some time after treatment with arsphenamin, and he decided that there is probably no causal relation.

It will be noted that all the foregoing cases had been diagnosed pernicious anemia and only in a few instances was there any mention of syphilis. Other than these reports we have been unable to find any series which dealt primarily with the effect of arsphenamin on anemia associated definitely with syphilis. Hirschfeld (1918) makes

the general statement, however, that in a few cases syphilis in its tertiary stage may present the symptom-complex of pernicious anemia. Treatment of syphilis, preferably with arsphenamin, "cures the disease, without a remission." Each patient with a positive Wassermann reaction, however, should not be regarded as syphilitic. Old syphilis is more often an associate than a cause of pernicious anemia. Hirschfeld has repeatedly seen cases of this type in which treatment was given for syphilis without success. The question concerning the syphilitic etiology is determined only by the success of specific therapy. It is always possible that the anemia has progressed so far that in spite of the control of the syphilis a normal regeneration of blood can no longer take place. This must be considered, particularly if during treatment the Wassermann reaction becomes negative and the blood findings are not improved.

EFFECT OF ARSPHENAMIN ON THE BLOOD PICTURE

Numerous investigators have studied the blood picture of syphilities under treatment with arsphenamin. In most cases the examinations were routine and made without particular reference to anemia. Lévy-Bing, Duroeux and Dogny, however, confined their reports to cases presenting definite anemia.

Von Besaiss, in 1911, noted, besides a hyperleukocytosis, marked increase in erythrocytes under arsphenamin treatment. In one case of tertiary syphilis the erythrocytes were unaltered, and in this case the preparation failed therapeutically.

Magat, in 1910, studied the blood and urine in three cases of recurrent fever, fifteen of syphilis and several of malaria treated by Georgyewsky. He speaks of the increase in erythrocytes and in hemoglobin with a decrease in leukocytes the first day after injection of arsphenamin.

Evdokimow, in 1911, observed a more or less distinct improvement in the blood picture under arsphenamin. The fluctuation in hemoglobin was transitory and rarely exceeded 8 per cent. Usually there was a slight increase in erythrocytes, a more or less marked leukocytosis with increase in eosinophils and a more frequent increase in neutrophils.

Baugher and Vaughan, in 1911, treated eighteen patients with syphilis, the erythrocytes and hemoglobin showing no constant change. There was an initial drop in leukocytes in the first few hours after the injection, a rapid increase during the first twenty-four hours, reaching a maximum in from two to four days, becoming normal or slightly above normal in from six to ten days.

Dorn, in 1912, stated that following intravenous injection of arsphenamin there is a hemolysis of short duration, with a decrease in hemoglobin, sometimes as great as 20 per cent, and a drop in

erythrocytes with the presence of urobilinogen and urobilin in the urine. The blood count returns to its former level or even a little higher in twenty-four hours.

Thevenot and Brissaud (1912) believe that arsphenamin causes an excitation of hematopoiesis. The erythrocytes show at first a diminution of sometimes 1,000,000. In fifteen days there is an increase of from 500,000 to 2,400,000.

Schwaer, in 1912, treated twenty-four syphilitic patients with positive Wassermann reactions whose blood pictures varied but little from normal. The hemoglobin showed but little change, from 5 per cent to 10 per cent either way, usually down, irrespective of the dose, 0.2 gm. to 0.6 gm. There was no definite alteration in the erythrocytes. Schwaer used small doses, 0.05 gm., in anemias of different etiology with practically no effect, and concludes that as then employed arsphenamin did not seem to have a place in the treatment of diseases of the blood in general.

MacKee, in 1912, investigated twenty-one cases before and after treatment and noted a very definite relation between the systemic reaction and the fall in erythrocytes, when, as he believed, the reactions were produced by the use of stale distilled water. In his opinion arsphenamin itself plays no part in reducing the count, for if there was no systemic reaction there was no substantial reduction in the number of erythrocytes and no reaction occurred with proper technic.

Lévy-Bing, Durocux and Dogny used from one to three injections of 0.3 gm. of arsphenamin in neutral suspension in ten cases of secondary syphilis. All the patients were moderately anemic, 3,200,000 to 3,800,000 erythrocytes. No appreciable change in hemoglobin was noted. There was a varying diminution in erythrocytes, 300,000 to 500,000, returning to the former count. There was no amelioration of the preëxisting anemia.

Wawiorowski, in 1912, using subcutaneous and intravenous injections of arsphenamin, found only a slight effect on hemoglobin and erythrocytes.

Heden (1913) gave from three to eight intravenous injections (average six of 0.4 gm. arsphenamin or its equivalent) in fifteen cases. After the first treatment there was a slight decrease in hemoglobin, 10 per cent at most, less after the second and third treatments and none later. The same held true for erythrocytes.

Yakimoff, in 1911, from experimental work on rats, normal or infected with *Spirochæta duttoni* and *Trypanosoma gambiense*, concludes that arsenobenzol causes first an inhibition of the hematopoietic organs and later an excitation. The reaction in monkeys is similar.

Kolmer and Yagles' work (1920) on the hemolytic activity of solutions of arsphenamin and neoarphenamin shows that hemolytic activity depends on (1) the direct action of arsphenamin, (2) the

use of nonisotonic solvents, and (3) the use of sodium hydroxide, especially in excess of that needed to produce the disodium arsphenamin salt.

It appears from the foregoing *resume* that of nine clinical investigators six report favorable results from arsphenamin in anemia, one is opposed to the treatment and two are undecided or give qualified opinions. Among investigators of the laboratory aspects of the problem of the influence of arsphenamin on the blood, five are in favor of the drug as a means of producing a rise in hemoglobin and erythrocytes and seven are against or give qualified opinions. In general it appears that there is a transient destruction of erythrocytes followed by a rise whose degree and permanence vary in different opinions.

CASES OBSERVED IN THE MAYO CLINIC

During the last four years approximately 4800 patients with syphilis have been treated in the Section on Dermatology and Syphilology of the Mayo Clinic. These are largely patients with late or latent syphilis who have come to the Clinic on account of nervous, cardiac or gastric symptoms, although there is a fair percentage with primary or secondary manifestations. In the examination of the records of these patients it was found that in the majority the hemoglobin was 70 per cent or more. It seemed advisable to study only those with 55 per cent or less. Only twenty-five patients were available for such a study. These were all patients in whom the diagnosis of syphilis was either unquestionable or in whom it was sufficiently plausible to warrant a therapeutic test. Patients with proved or suspected syphilis were chosen because if arsphenamin will help any type of anemia it should help the type with a possible syphilitic basis.

Three types of cases are possible in this group of anemias:

Type 1, true pernicious anemia, giving a nonspecific positive Wassermann reaction.

Type 2, true pernicious anemia in association with syphilis.

Type 3, severe anemia due directly or indirectly to syphilis.

Cases were regarded as proved syphilitic, in which there was at least a definite history, a positive Wassermann test and remnants of an old infection or signs at the time of examination of involvement in any system. Cases in which there was either no history or only a doubtful history of a primary lesion, with no clinical evidence of syphilis, or in which only one positive Wassermann reaction had been obtained were regarded as doubtful. Cases were classified as a pernicious type of anemia in which the blood picture showed a decrease in erythrocytes out of proportion to the fall in hemoglobin with the presence of anisocytosis, poikilocytosis, nucleated erythrocytes and clinically by weakness, dyspnea, sore-tongue, gastro-

intestinal disturbances, pigmentary changes (lemon tint) and sometimes nervous manifestations. Obviously little may be expected in the first two groups from treatment for syphilis, *per se*, except insofar as the drugs used primarily against syphilis may also have a direct beneficial effect on the anemia, either by stimulating hematopoiesis or by preventing blood destruction.

METHODS AND TREATMENT

Schamberg's preparation of arsphenamin, obtained from the Dermatological Research Laboratories, Philadelphia, was used in most cases in increasing doses, 0.3 gm. to 0.5 gm., at weekly intervals. In a few cases Lowey's solution of arsphenamin was used. Novarsenobenzol was substituted when the patient's condition indicated. Occasionally the dosage was reduced. After the patient had been given a course of six injections, during which time his tolerance for mercury was ascertained, he was sent home for from one to three months with or without mercurial treatment in the form of 4 gm. 33 per cent inunctions, or *hydrargyrum cum creta*. Second and even third courses were given to some of these patients.

Transfusions were given to certain patients prior to, concomitant with, or following specific therapy. They were given by the citrate method, the donor and recipient usually belonging to the same group, although in emergency a Group IV donor was used irrespective of the recipient's group. The usual quantity given was 500 cc.

The Dare hemoglobinometer was used throughout. The recent work of Senty, in which he showed that readings above 70 per cent were subject to error, needs mention. Below this, however, the estimations are accurate. In this series, then, the readings may be considered correct apart from the variations due to personal equation. We have arbitrarily taken increases or decreases of 5 per cent as legitimate error and have paid attention only to greater changes.

The Wassermann technic as carried out at the Clinic under the direction of Dr. A. H. Sanford is a slight modification of the original Noguchi system. In the preparation of the amboceptor, dogs instead of rabbits have been used. Human corpuscles have been sensitized by adding a definite amount of amboceptor to the washed corpuscles and placing the mixture overnight in the ice-box. The sensitized cells are then titrated against various amounts of 40 per cent diluted guinea-pig serum. The standard antigen for routine work is an acetone-insoluble fraction of heart extract.

We have been more interested in the effect of arsphenamin on the course of anemia from day to day and from week to week than in the immediate effect on the blood picture. No attempt has been made to learn whether there was an initial drop in the first few minutes or hours with a subsequent rise to the original count or

above. This has been the object of study by several investigators, and the results have been uniform.

Tables 1, 2, and 3 classify our material from various standpoints.

TABLE I.—EVIDENCE OF THE PRESENCE OF SYPHILIS IN RELATION TO THE BLOOD PICTURE

Evidence of syphilis.	Pernicious anemia.	Secondary anemia.	Undetermined,[1] (hemoglobin only.)	Total.
Indisputable	5	5	1	11
Wassermann test and history	1	1		2
Wassermann test only	6	3	1	10
History only	1	..	..	1
No history. Wassermann test negative	..	1	..	1
	13	10	2	25

It will be seen that about half the cases in this series presented the picture of pernicious anemia. A positive Wassermann reaction as the only evidence of syphilis was encountered twice as frequently in pernicous anemia as in secondary anemia, perhaps supporting the theory that this disease may of itself yield a positive Wassermann reaction in the absence of syphilis (Sanford).

TABLE II.—CLINICAL DIAGNOSIS

Pernicious anemia:	
Definite	6
Probable	4
Atypical	1
Associated with gastric syphilis	1
Associated with hepatitis and cutaneous tertiary syphilis	1
	13
Secondary anemia:	
Anemia prominent	3
Associated with hereditary syphilis	1
Associated with aortitis	1
Associated with gastric syphilis	1
Associated with syphilitic splenomegaly and enlarged liver	1
Associated with chronic arthritis	1
Associated with gastric syphilis and osteitis	1
Associated with periostitis (syphilis of the ribs?) and empyema	1
	10
Undetermined (hemoglobin estimation only) (clinically secondary in type):	
Tabes dorsalis	1
Hypertension	1
	2

In cases presenting the picture of pernicious anemia the anemia was the outstanding feature and only infrequently were other conditions suggesting syphilis present. Secondary anemia, however,

[1] Clinically secondary in type.

was more commonly associated with some syphilitic involvement of other systems.

TABLE III.—THE EFFECT OF TREATMENT FOR SYPHILIS ON SEVERE ANEMIAS

	Pernicious anemia.	Secondary anemia.	Total.
Patients received mercury	9	9	18
Patients with proved syphilis	3	6	9
Patients sent home on mercury treatment	7	2	9
Patients with proved syphilis	2	1	3
Patients sent home on mercury treatment, hemoglobin fell from 12 per cent to 35 per cent	4		4
Patients with proved syphilis	2		2
Patients received arsphenamin	13	12[2]	25
Patients with proved syphilis	5	6	11
Patients without change under arsphenamin	3	6	9
Patients with proved syphilis	1	5	6
Patients improved under arsphenamin	5	5[2]	10
Patients with proved syphilis	2	1	3
Patients became worse under arsphenamin	5	1	6
Patients with proved syphilis	2		2

Mercury was given with arsphenamin and therefore it was often difficult to estimate its effect, which is best judged by watching the results when it is given to patients during their rest period between courses of intravenous injections. In four of nine patients a reduction in hemoglobin of from 12 to 35 per cent and a decrease in erythrocytes of from 500,000 to 2,000,000 were noted under injections. In all of these patients showing a decrease the blood picture had approached that of pernicious anemia from the start. They had previously improved from 18 per cent to 30 per cent under arsphenamin therapy. The relapses may, of course, have been purely a coincidence. While long experience may have shown mercury to be "the iron of syphilitic anemia," it must evidently be used with caution in the more severe grades, particularly when the picture approximates that of primary pernicious anemia. In two of the patients who reacted unfavorably to mercury, arsphenamin barely maintained the blood picture, while transfusions maintained it at a slightly higher level. One patient's hemoglobin continued to fall from 56 per cent to 36 per cent under three arsphenamin injections, but one month after a single transfusion the hemoglobin had risen to 67 per cent, the erythrocytes to 4,280,000, giving an index of 0.7, compared with hemoglobin 36 per cent, erythrocytes 1,530,000, and an index of 1.1. The fourth patient was apparently improving

[2] Including two indeterminate cases (hemoglobin only) clinically secondary, one with definite syphilis.

under arsphenamin therapy when a reaction, following an intravenous injection of the drug, resulted in a rapid decline, and only by repeated transfusions was the hemoglobin raised from 33 per cent to 46 per cent and the erythrocytes from 1,750,000 to 2,510,000. It is apparent at least that the patients reacting unfavorably to mercury showed evidence of a tendency to an unfavorable course.

With regard to the effect of arsphenamin in our series the drug has been given with reasonable safety even in patients whose hemoglobin is 20 per cent, although it seems a better policy to increase this to 30 per cent by transfusions, if possible, before starting specific therapy. Every precaution must be taken to prevent reactions, for accidents which may be only disagreeable in otherwise healthy persons assume dangerous proportions in persons whose condition is already grave.

In six cases a drop in hemoglobin of from 10 per cent to 20 per cent and a decrease of about 500,000 erythrocytes occurred during arsphenamin therapy. To these may be added one case in which an increase had previously been shown following intravenous therapy. In two of these unfavorably affected cases transfusions were of no value. In another the blood count continued to drop for a time even with transfusions, but ultimately, after seven transfusions, the picture improved. The hemoglobin in this case rose from 18 per cent to 48 per cent and the erythrocytes from 1,470,000 to 3,150,000. Despite this improvement the patient died shortly after reaching home. An initial drop in hemoglobin from 70 per cent to 50 per cent with a decrease in the number of erythrocytes from 4,600,000 to 4,000,000 was observed in the fourth case following two injections of arsphenamin. Throughout three subsequent courses in this case the erythrocytes fluctuated between 3,000,000 and 4,000,000 and the hemoglobin between 50 per cent and 60 per cent. In the fifth and sixth cases there was a 5 per cent increase in hemoglobin but a decrease of 500,000 erythrocytes. One of these patients died shortly after transfusion.

In nine cases no definite effect from arsphenamin was noted. Two of the patients received only three injections, a toxic erythema in one rendering it necessary to discontinue the arsenic preparation. The other presented the blood picture of such an advanced pernicious anemia that a transfusion was given but without improvement. He returned home and a letter indicated that his condition was unchanged. Seven patients received from four to fourteen injections without definite effect. Two of these had pernicious anemia with a questionable syphilis and five had secondary anemia; all but one of the latter were proved to be syphilitics.

In ten patients an improved blood picture (an increase of from 8 per cent to 35 per cent in hemoglobin and from 200,000 to 2,000,000

in erythrocytes) followed arsphenamin treatment. Five of them had pernicious anemia. In only three of the ten who improved was the evidence of syphilis indisputable. We are surprised in comparing this group with the foregoing to find the relatively high proportion of patients with pernicious anemia and the relatively small proportion with proved syphilis.

Transfusions were resorted to at some period of the treatment of sixteen patients, either to reinforce those who had made only moderate improvement or as treatment for those who had not responded. If patients did not improve under arsphenamin treatment only it was often combined with transfusion, and later transfusions were given alone. In patients whose initial hemoglobin was 25 per cent or under transfusions were used to bring the hemoglobin above 30 per cent. The estimation of the relative value of arsphenamin and transfusions is more difficult in cases in which the transfusions had been resorted to during the arsphenamin course. For example, one patient during the second course received four injections of arsphenamin and three of novarsenobenzol. Transfusions were given before the first and fourth injections. The hemoglobin at the beginning was 30 per cent and at the end 49 per cent, with a reading of 64 per cent following the second transfusion. Arsphenamin had no appreciable effect during the first and third courses. We therefore would feel justified in this case in concluding that the rise was merely due to the temporary beneficial effect of the transfusions rather than that the subsequent arsphenamin injections had counteracted the good effect of the transfusions.

In four instances transfusions gave more gratifying results than did arsphenamin. One of these patients had continued to improve under arsphenamin, the hemoglobin increasing from 40 per cent to 70 per cent. He relapsed under mercury and the third course of arsphenamin sufficed only to hold the hemoglobin at 40 per cent. By repeated transfusions the hemoglobin was maintained between 45 per cent and 50 per cent. In a similar case the hemoglobin dropped from 70 per cent to 56 per cent under mercury and continued to drop from 56 per cent to 36 per cent under arsphenamin. One month after a single transfusion the hemoglobin was 67 per cent. Another patient's hemoglobin improved under specific treatment from 35 per cent to 45 per cent. After receiving a transfusion the patient was sent home. In two months his hemoglobin estimation read 75 per cent, and this was maintained during the next course of arsphenamin. The fourth patient received one course of arsphenamin with slight improvement. Transfusions were combined with arsphenamin during the second course. After the second injection of the third course he had a violent reaction with a rapid fall in hemoglobin. Repeated transfusions raised the hemoglobin from 33 per cent to 46 per cent and the erythrocytes from 1,750,000 to 2,510,000.

In three other cases transfusions improved the blood picture, but the patients died. Transfusion had no effect in four instances and only a temporary beneficial effect in two. In another case following a relapse transfusions were successful in maintaining the count at a higher level, but not so high as it had been previously. In two cases transfusions were used with success before beginning specific therapy.

If, as Hirschfeld says, the proof that a pernicious type of anemia is due to syphilis depends on cure without remissions by means of treatment of the syphilis, no cases of syphilitic pernicious anemia have been recognized in the Mayo Clinic since the organization of the Section of Dermatology and Syphilology. The nearest approach to such a case is that of a man, aged thirty-eight years, with a history of infection and with leukoplakia in the mouth. His spinal fluid and his blood Wassermann test were negative, even with a provocative test. His symptoms and findings, interpretated by several competent observers, were those of a typical primary anemia. His hemoglobin was 55 per cent, the erythrocytes numbered 2,560,000, with a color index of 1. After three transfusions the hemoglobin estimation was 70 per cent with 4,000,000 erythrocytes and an index of 0.8. After two courses of intravenous therapy the patient had 4,750,000 erythrocytes and 85 per cent hemoglobin, and following the third course the erythrocytes increased to 5,040,000. He is the picture of health, has gained 50 pounds and has been well for two and one-half years. Whether his improvement was due to transfusion or to the arsphenamin injections, and whether he is merely having a long remission, cannot be stated. Stockton (1919) recently reported a case of pernicious anemia in which the patient had a remission after twelve years of apparently good health

SUMMARY AND CONCLUSIONS

1. Severe anemia, either primary or secondary, associated with late or latent syphilis, is apparently rare, twenty-five cases appearing in approximately 4800 records in the Section on Dermatology and Syphilology in the Mayo Clinic.

2. Pernicious anemia may be seen in association with syphilis, but no case exhibiting an incontestable etiologic connection has appeared in our records.

3. One patient with the clinical picture of pernicious anemia and a doubtful syphilitic infection has been apparently well two years as a result of treatment.

4. Pernicious anemia in the apparent absence of syphilis may yield a positive serum Wassermann reaction.

5. Mercury by inunction, used alone, produced an unfavorable reaction in four of nine patients with anemias who had pre-

viously improved under arsphenamin, but all had primary anemia and subsequently showed evidences of a relapsing unfavorable course.

6. We believe, therefore, that in syphilis with anemia mercury should be used with caution, especially if the picture suggests the primary type.

7. Five of thirteen patients with primary anemia improved under arsphenamin. Of these two who improved and three who did not had demonstrable syphilis.

8. Five of thirteen patients with primary anemia became worse under arsphenamin; of these two had syphilis.

9. Five of twelve patients with secondary anemia improved under arsphenamin treatment. Of these only one who improved and five who did not had demonstrable syphilis.

10. Only one of twelve patients with secondary anemia became worse under arsphenamin.

11. In our experience, then, arsphenamin has been much more effective in secondary anemia than in primary anemia, but curiously disappointing in secondary anemia with associated manifestations of syphilis.

12. Twelve of sixteen patients improved under transfusion, four of them after arsphenamin had failed. Two of these patients showed only temporary improvement and three others died notwithstanding the improved blood picture. The effect of transfusion could only be judged with difficulty because of the conditions under which it was employed.

13. In four of sixteen cases transfusion was without effect.

14. Transfusion should be a preliminary to arsphenamin when the hemoglobin is below 20 per cent.

15. Reactions to arsphenamin injections must be carefully avoided since they may produce an alarming drop in hemoglobin.

16. No satisfactory rule for determining which case would improve on treatment for syphilis and which case would not could be arrived at. In general half the cases may be expected to improve.

17. The degree of improvement is not necessarily proportional to the demonstrability of syphilis. The pernicious anemia associated with undoubted syphilis which we have seen has run the ultimate course of pernicious anemia regardless of treatment for syphilis.

18. Hemoglobin estimations alone are not sufficient to indicate the progress of the patient. The hemoglobin may rise and the number of erythrocytes fall at the same time.

19. Arsphenamin treatment is safe if carefully used in anemia and should be employed in patients with undoubted evidence of the disease, and, as a therapeutic test, when reasonable suspicion of its presence exists.

20. Transfusion must remain the ultimate resort in primary

eases, and in those cases associated with syphilis in which arsphenamin has failed, even in the presence of syphilis, the best effect will be secured by both together.[3]

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[3] Another eoso in the Moyo Clinic was brought to our attention nfter the completion of the poper. As it does nat alter nny of the eonclusions we have not thought it advisnble to recost the ortiele.

The case is one of definite syphilis with hepatic cirrhosis and splenomegaly. Weekly tappings were necessary. The blood picture was that of a moderate anemia, with hemoglobin 08 ond erythrocytes 3,980,000. After n six weeks' course of mercury inunctions with potassium iodide by mouth, the patient improved greatly and did not require tapping thraughout this perind. His hemoglobin, however, dropped to 59 per cent und his erythrocytes ta 2,880,000. Tha improvement in his general condition continued through three months' trentment with *hydrargyrum cum creta* nnd with potassium iodide. A course af arsphenamin, 0.2 ta 0.4 gm., was given, at the end of which time the hemoglobin had risen ta 60 per cent and the erythrocytes to 4,500,000. Splenectomy was tben perfarmed. The patient died early the next morning.

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LEUKEMIA IN CHILDREN, WITH SPECIAL REFERENCE TO LESIONS IN THE NERVOUS SYSTEM.

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The recent occurrence of two rather unusual cases of leukemia in children admitted to the pediatric service of the Mount Sinai Hospital has prompted me to go over the hospital records of the past ten years and to collect therefrom the cases of leukemia admitted during that time. In tabulating these cases, twenty-three in number, several interesting points are brought out and seemed to me worth while recording. It is distinctly not my purpose to review all the symptoms and signs of leukemia as this disease occurs in children, as this has been ably done by others, especially by Benjamin and Sluka in their monograph *Die Leukæmie im Kindesalter*, 1907, and by A. Stranch in an article published in the *American Journal of the Diseases of Children* in 1913, where a good bibliography may be found. In the review of the cases in the present paper I shall therefore not make any attempt at completeness in describing leukemia clinically, but will stress especially the following points: (1) The type of disease as it attacks children; (2) the common physical findings; (3) the diagnosis of the disease; (4) the symptoms referable to the nervous system.

As our cases well show, leukemia in children is essentially an acute disease. The longest duration of any of our cases was one year (Case 22). Benjamin and Sluka refer to a chronic case of the myeloid variety which lasted two years. All the cases which last